Proposed Registration Decision PRD2015-01

BLAD Polypeptide

(publié aussi en français)

6 February 2015

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6604-E2
Ottawa, Ontario K1A 0K9

Internet: pmra.publications@hc-sc.gc.ca
healthcanada.gc.ca/pmra
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra.infoserv@hc-sc.gc.ca

Canada

ISSN: 1925-0878 (print)
1925-0886 (online)

Catalogue number: H113-9/2015-1E (print version)
H113-9/2015-1E-PDF (PDF version)

© Her Majesty the Queen in Right of Canada, represented by the Minister of Health Canada, 2015

All rights reserved. No part of this information (publication or product) may be reproduced or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, or stored in a retrieval system, without prior written permission of the Minister of Public Works and Government Services Canada, Ottawa, Ontario K1A 0S5.

Table of Contents

Overview 1
Proposed Registration Decision for BLAD Polypeptide 1
What Does Health Canada Consider When Making a Registration Decision? 1
What Is BLAD Polypeptide? 2
Health Considerations 2
Environmental Considerations 4
Value Considerations 4
Measures to Minimize Risk 4
Next Steps 5
Other Information 5
Science Evaluation 7
BLAD Polypeptide 7
1.0 The Active Ingredient, Its Properties and Uses 7
1.1 Identity of the Active Ingredient 7
1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product 7
1.3 Directions for Use 8
1.4 Mode of Action 9
2.0 Methods of Analysis 9
2.1 Methods for Analysis of the Active Ingredient 9
2.2 Method for Formulation Analysis 9
2.3 Methods for Residue Analysis 9
2.4 Methods for Determination of Relevant Impurities in the Manufactured Material 9
3.0 Impact on Human and Animal Health 9
3.1 Toxicology Summary 9
3.2 Occupational and Bystander Risk Assessment 11
3.2.1 Toxicological Endpoints 11
3.2.2 Use Description 11
3.2.3 Mixer, Loader, and Applicator Exposure and Risk 11
3.2.4 Post-application Worker Exposure and Risk 12
3.2.5 Residential and Bystander Exposure and Risk 12
3.3 Food Residue Exposure Assessment 12
3.3.1 Food and Drinking Water 12
3.3.2 Maximum Residue Limits 13
4.0 Impact on the Environment 13
4.1 Fate and Behaviour in the Environment 13
4.2 Environmental Risk Characterization 14
5.0 Value 14
5.1 Acceptable Claims and Effectiveness Against Pests 14
5.2 Consideration of Benefits 16
5.3 Economics 16
5.4 Sustainability 16
5.4.1 Survey of Alternatives 16
5.4.2 Compatibility with Current Management Practices Including Integrated Pest Management 16

5.4.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance 16
5.4.4 Contribution to Risk Reduction and Sustainability 17
6.0 Pest Control Product Policy Considerations 17
6.1 Toxic Substances Management Policy Considerations 17
6.2 Formulants and Contaminants of Health or Environmental Concern 17
7.0 Summary 18
7.1 Human Health and Safety 18
7.2 Environmental Risk 18
7.3 Value 19
8.0 Proposed Regulatory Decision 19
List of Abbreviations 21
Appendix I Tables and Figures 23
Table 1 Toxicity Profile of Problad Plus Containing BLAD Polypeptide 23
Table 2 Toxicity Profile of Problad Technical Fungicide 24
Table 3 Registered Alternative Products for the Crops and Pests to be Registered on the Problad Plus Label 26
Table 4 Use (Label) Claims Proposed by Applicant and Whether Acceptable or Unsupported 29
References 31

Overview

Proposed Registration Decision for BLAD Polypeptide

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Problad Technical Fungicide and Problad Plus, containing the technical grade active ingredient BLAD polypeptide, to be used against powdery mildew and grey mould on grape, strawberry, tomato, stone fruit, almond and ornamental plants.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Problad Technical Fungicide and Problad Plus.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

---

1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on BLAD polypeptide, the PMRA will consider any comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on BLAD polypeptide, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is BLAD Polypeptide?

BLAD polypeptide is a fragment of a naturally occurring seed storage protein in sweet lupine (*Lupinus albus*) that serves as a nitrogen source for the germinating and developing plant. It also acts on susceptible fungal pathogens by causing damage to the fungal cell wall and disrupting the inner cell membrane. BLAD polypeptide is not yet classified by the Fungicide Resistance Action Committee, but based on the proposed mode of action, the risk of resistance is considered to be small.

Health Considerations

Can Approved Uses of BLAD Polypeptide Affect Human Health?

BLAD polypeptide is unlikely to affect human health when it is used according to label directions.

Potential exposure to BLAD polypeptide may occur when handling and applying the end-use product, Problad Plus. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

In laboratory animals, the acute toxicity of the end-use product, Problad Plus, containing BLAD polypeptide, was low via the oral, dermal, and inhalation routes of exposure. Problad Plus is mildly irritating to the skin and eyes; consequently, the hazard signal words "CAUTION EYE AND SKIN IRRITANT" are required on the Problad Plus label. Problad Plus is not a dermal sensitizer.

A request to bridge acute toxicity data from the end-use product to the technical grade active ingredient was considered to be acceptable. The active ingredient, BLAD polypeptide, was considered to be of low acute toxicity via the oral, dermal, and inhalation routes of exposure. BLAD polypeptide was mildly irritating to the skin and eyes; consequently, the hazard signal

---

[3] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

[4] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

words "CAUTION EYE AND SKIN IRRITANT" are required on the Problad Technical Fungicide label. BLAD polypeptide is not a dermal sensitizer.

BLAD polypeptide is not expected to cause effects in developing young or to cause damage to genetic material when used according to the label instructions.

BLAD polypeptide is not expected to elicit an allergic response in individuals who are sensitive to allergens present in lupine seeds and/or other legumes. In addition, all products manufactured for import into Canada will be required to ensure the absence of primary allergen components (in other words, levels are below the level of detection).

The risk assessment protects against the effects of BLAD polypeptide by ensuring that the level of human exposure is well below the lowest dose at which effects occurred in animal tests.

Risks in Residential and Other Non-Occupational Environments

Estimated risk for non-occupational exposure is not of concern provided that directions specified on the label are observed.

Residential exposure to individuals coming in contact with Problad Plus from drift during application is not expected to result in unacceptable risk when Problad Plus is used according to label directions.

Occupational Risks From Handling and Applying Problad Plus

Occupational risks are not of concern when Problad Plus is used according to the proposed label directions, which include protective measures.

An assessment conducted for individuals handling and applying Problad Plus indicated that the risk is not of concern when the product is used according to label directions.

Residues in Water and Food

Dietary risks from food and drinking water are not of health concern.

Dietary risks from food and drinking water are expected to be negligible given the low toxicity, the lack of quantifiable residues from the supplemental residue information, and the likelihood (most likely negligible) that exposure of individuals to Problad Plus with lupine and/or other legume (for example, peanut) sensitivities will result in an allergic reaction. Consequently, the specification of a maximum residue limit under the *Pest Control Products Act* is not being recommended.

Environmental Considerations

What Happens When Problad Plus Is Introduced Into the Environment?

Problad Technical Fungicide will enter the environment when applied as Problad Plus to grapes, strawberries, tomatoes, stone fruit, and ornamentals. Problad Technical Fungicide will dissipate in the environment primarily through microbial degradation. The risk to non-target aquatic and terrestrial organisms in the environment is negligible.

BLAD is a naturally-occurring seed storage protein, which accumulates exclusively in the cotyledons of Lupinus species (for example, *Lupinus albus*), between days four and twelve after the onset of germination. It is a 20kDa polypeptide of β-conglutin, or characterized as a fragment of the amino acid sequence of β-conglutin. Th β-conglutin protein is classified as a 7S globulin which is part of the broader family of cupin proteins, which provides a major nitrogen source for germination of the developing plant.

Problad Plus is a non-systemic biofungicide with strong antifungal activities both preventive but also for control. The non-toxic mode of action is described as binding very strongly to chitin in fungal cell walls, inhibiting any fungal growth. The active ingredient degrades chitin by catalyzing the successive removal of the *N*-acetyl-D-glucosamine terminal chitin monomers, and destroying the fungal cells.

Problad TGAI is readily biodegradable and non-toxic to all non-target organisms tested, both terrestrial and aquatic. Therefore, the risk to non-target aquatic and terrestrial organisms in the environment is negligible when Problad Plus is used according to the label directions.

Value Considerations

What Is the Value of Problad Plus?

Problad Plus is a broad spectrum biological fungicide with a unique mode of action that will contribute to resistance management when integrated with cultural methods and chemical sprays in an Integrated Pest Management program.

Problad Plus provides non-systemic, preventative action when applied to plant foliage with activity against powdery mildew and grey mould on fruit, vegetable and ornamental crops and blossom blight on stone fruit.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Problad Plus to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Both Problad Technical Fungicide and Problad Plus labels must include the statement, "CAUTION – SKIN AND EYE IRRITANT" on the principal display panel and "May irritate skin and eyes" and "Avoid contact with the skin and eyes" on the secondary display panel.

To avoid direct contact with Problad Plus on the skin and eyes, workers involved in the mixing, loading, application, cleaning, and maintenance of machinery must wear long-sleeved shirts, long pants, chemical-resistant gloves, shoes, socks, and protective eyewear.

To avoid inadvertent bystander exposure during application, the Problad Plus label must include the statement, "Apply only when the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools, and recreational areas is minimal. Take into consideration wind speed, wind direction, temperature, application equipment, and sprayer settings."

Environment

No further mitigation measures are required at this time.

Next Steps

Before making a final registration decision on BLAD polypeptide, the PMRA will consider any comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document.

Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on BLAD polypeptide (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

BLAD Polypeptide

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	BLAD Polypeptide
Function	Fungicide
Chemical name	
1. **International Union of Pure and Applied Chemistry (IUPAC)**	Not applicable
2. **Chemical Abstracts Service (CAS)**	Not applicable
CAS number	Not applicable
Molecular formula	Not applicable
Molecular weight	Not applicable
Structural formula	Not applicable
Purity of the active ingredient	39.6%

1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

Technical Product—Problad Technical Fungicide

Property	Result
Colour and physical state	Dark brown liquid
Odour	Sweet-like
Melting range	Not applicable; the product is a liquid at room temperature.
Relative Density	1.256 g/mL
Oxidizing or Reducing Activity	Compatible with water, 10% monoammonium phosphate, iron powder and kerosene. Incompatible with 10% potassium permanganate
Flash Point	>100°C
Explodability	No shock sensitivity and no thermal sensitivity to explosion

Property	Result
Miscibility	Miscible in water
Corrosion Characteristics	Not corrosive to plastic
Viscosity	109.2 centistokes at 20°C 44.1 centistokes at 40°C
pH	6.32 at 22°C in 1% w/w aqueous solution
Stability (temperature)	BLAD polypeptide should be stored in a cool dry area.

End-Use Product—Problad Plus

Property	Result
Formulation Type	Suspension
Guarantee	20% BLAD polypeptide
Colour and Physical State	Dark brown liquid
Odour	Sweet-like
Melting range	Not applicable; the product is a liquid at room temperature.
Relative Density	1.255 g/mL
Oxidizing or Reducing Activity	Compatible with water, 10% monoammonium phosphate, iron powder and kerosene. Incompatible with 10% potassium permanganate
Flash Point	>100°C
Explodability	No shock sensitivity and no thermal sensitivity to explosion
Miscibility	Miscible in water
Corrosion Characteristics	Not corrosive to plastic
Viscosity	765.932 centistokes at 20°C 230.181 centistokes at 40°C
pH	6.38 at 22°C in 1% w/w aqueous solution
Stability (temperature)	Problad Plus should be stored in a cool dry area for a period of up to 6 months.

1.3 Directions for Use

Problad Plus is applied preventatively to plant foliage at rates of 1.5 – 3.3 L/ha. The product may be re-applied on 7 to 10 day intervals or according to phenological stages of growth. Higher rates and shorter intervals are to be used with high disease pressure. Up to five applications may be made per season up to and including the day of harvest.

1.4 Mode of Action

BLAD polypeptide inhibits fungal growth by binding to and degrading chitin, a major component of the fungal cell wall.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

Appropriate methodologies were provided to determine percent BLAD polypeptide, percent protein, percent carbohydrate, percent ash, percent lipid, percent lignin, percent phytic acid and percent water in Problad Plus.

2.2 Method for Formulation Analysis

An appropriate methodology was provided to determine the content of BLAD polypeptide in Problad Plus.

2.3 Methods for Residue Analysis

Enzyme Linked Immunosorbent Assay with a VersaMax plate reader (OD at 450 nm) (ELISA; EASI Method No.: RA029 for grape and strawberry; EASI Method No.: RA031 for tomato) was determined to be an appropriate methodology for residue analysis of BLAD polypeptide on food and feed crops treated with Problad Plus. These methods fulfilled the requirements with regards to specificity, accuracy, and precision at the respective limit of quantification (LOQ = 0.02 ppm). The average recovery for each matrix for the purposes of method validation ranged from 43.0% to 52.2%. Concurrent recoveries for BLAD polypeptide from grape, tomato, and strawberry samples averaged 44.8%, 69.8%, and 50.8% respectively.

2.4 Methods for Determination of Relevant Impurities in the Manufactured Material

An appropriate methodology was provided to determine the content of lupanine in Problad Plus. Lupanine is a naturally occurring alkaloid present in lupines.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for BLAD polypeptide was conducted by the PMRA.

The database for BLAD polypeptide is considered adequate (Tables 1 & 2, Appendix I), consisting of laboratory animal toxicity studies (acute oral, dermal, and inhalation toxicity, skin and eye irritation, and dermal sensitization), and rationales to waive short-term toxicity, prenatal developmental toxicity, and genotoxicity. A review of the scientific literature regarding the

potential allergenicity of BLAD polypeptide and the potential cross-reactivity of BLAD polypeptide with peanuts and other storage proteins was submitted. A serology study assessing the potential allergenicity and cross-reactivity of Problad Plus was also submitted. The toxicology and serology studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is such that the database is considered adequate to assess the toxicological hazards of these pest control products.

Problad Plus (20% w/w BLAD polypeptide) is of low acute oral, dermal, and inhalation toxicity, mildly irritating to the eyes and to the skin, and is not a dermal sensitizer. Studies were submitted to address the data requirements for the end-use product, Problad Plus, which contains the same percentage of active ingredient as the technical grade active ingredient, Problad Technical Fungicide. Since the inclusion of formulants in the end-use product is not expected to adversely affect the toxicology findings, the studies submitted for Problad Plus are acceptable as bridging data for Problad Technical Fungicide. The request to bridge the acute toxicity data from the end-use product to the technical grade active ingredient was considered to be acceptable.

Waivers were granted for the short-term toxicity, prenatal developmental toxicity, and genotoxicity based on the minimal exposure expected when label precautions are observed.

With increasing reports of allergy resulting from the use of lupine derived seed products in prepared foods, there was concern that the germinated sweet lupine seed extract in Problad Technical Fungicide and Problad Plus may also be allergenic. Based on informatics, susceptibility to protease digestion, and estimates of dietary intake, BLAD polypeptide is expected to be of low potential to cause allergic reactions and to cross-react with known allergens from other legumes, such as peanuts and soybean. This argument was further strengthened with results from a serology study which demonstrated that individuals sensitive to lupine and/or other legumes (for example, peanuts) are unlikely to, when exposed to Problad Plus, have an allergic reaction. As such, it is important to note that the proteins (conglutins) in lupine seed that are responsible for allergic reactions in sensitive individuals are not present in Problad Technical Fungicide or Problad Plus.

Since there are no human or companion animal health concerns, the formulants in Problad Plus are supported for the use on terrestrial food and feed crops, and ornamental plants outdoors.

The alkaloid lupanine, a contaminant identified and quantified (~ 0.003% w/w) during the product characterization and analysis review, is not expected to be a health concern.

All products manufactured for import into Canada will be required to ensure that the primary allergen components continue to be absent (in other words, below the level of detection).

Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the mandatory reporting of incidents can be found on the PMRA website. Incidents from Canada and the United States were searched and reviewed for BLAD polypeptide. As of 4 November 2014, there were no incident reports submitted to the PMRA, United States Environmental Protection Agency or California Environmental Protection Agency.

3.2 Occupational and Bystander Risk Assessment

3.2.1 Toxicological Endpoints

Occupational exposure to Problad Plus is characterized as short-term and is predominately by the dermal and inhalation routes. Problad Plus (20% w/w BLAD polypeptide) is mildly irritating to the eyes and to the skin.

3.2.1.1 Dermal Absorption

Dermal absorption of BLAD polypeptide is not expected to be of concern due to the large size of the polypeptide molecules (MW > 500) and its low toxicity via the dermal route.

3.2.2 Use Description

Problad Plus will be used on grapes, strawberries, tomatoes, stone fruit, and outdoor ornamentals. The method of application is by spray equipment commonly used for making ground applications (groundboom, airblast, and handheld equipment). The maximum amount of the active ingredient handled is calculated to be 298.19 kg/day by custom groundboom. Problad Plus has an application interval of 7 to 10 days and a maximum of 5 applications per season. The post-application activities are expected to be typical for agricultural crops (for example, scouting of treated areas).

The potential for occupational exposure of workers will be minimized when workers observe the precautionary statements on the label, and the subsequent risk is considered acceptable.

3.2.3 Mixer, Loader, and Applicator Exposure and Risk

Exposure to workers mixing, loading, and applying Problad Plus is expected to be short-term in duration and to occur primarily by the dermal and inhalation routes.

Since Problad Plus is mildly irritating to the skin and eyes, the personal protective equipment (PPE) label statements should include the use of a long-sleeved shirt, long pants, chemical-resistant gloves, shoes, socks, and protective eyewear.

The risk due to exposure from mixing, loading, applying, clean-up, and maintenance of machinery for workers is considered to be acceptable when used according to the label, which includes adhering to the label precautions.

3.2.4 Post-application Worker Exposure and Risk

There is a potential for exposure to workers re-entering areas treated with Problad Plus. Given the nature of the post-application activities typically performed (for example, scouting treated areas), dermal contact with treated surfaces is possible, as well as inhalation of dislodged material that has dried on the treated crops. While the degree of exposure will be related to the time of re-entry and the duration of the activities, the potential risk due to exposure resulting from post-application work is not a concern, regardless of the type and duration of the activity.

3.2.5 Residential and Bystander Exposure and Risk

The application of Problad Plus near residential areas may result in the exposure of residents. A residential area is defined as a location where bystanders, including children, may be exposed during or after application. These locations include around homes, schools, parks, playgrounds, playing fields, public buildings or any other area where the general public, including children, could be exposed.

In order to minimize drift, and subsequent risk due to bystander exposure, when applying Problad Plus, wind speed, wind direction, temperature, application equipment, and sprayer settings should be considered.

3.3 Food Residue Exposure Assessment

3.3.1 Food and Drinking Water

The enzyme-linked immunosorbent assay (ELISA) was used to assess BLAD polypeptide residues on grapes and tomatoes and considered to be acceptable as an analytical methodology (LOQ = 0.02 ppm and LOD = 0.005 ppm).

Studies submitted to address the residue trial and residue decline requirements were performed in California, which did not fully address the residue trials required for the Canadian Zones. However, these studies were considered to be supplemental since they did provide information that was considered during a weight of evidence approach. That is, after five broadcast foliar applications of Problad Plus to grapes, strawberries, and tomatoes at the maximum application rate (871 g/ha), no quantifiable residues of the active ingredient, BLAD polypeptide, were found even at 0 days after the last application. At 5X the maximum application rate (4.355 kg/ha), 2/2 samples showed quantifiable residues (0.025 to 0.028 ppm) in strawberries at 0 and 1 day after the last application, however, by the third day after the last application, all residue samples were below the LOQ. The measured half-life was two days.

An acceptable preharvest interval was determined to be up to and including the day of harvest (in other words, a preharvest interval of 0 days).

3.3.2 Maximum Residue Limits

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine that the consumption of the maximum amount of residues that are expected to remain on food products when a pesticide is used according to label directions will not be a concern to human health. This maximum amount of residues expected is then legally specified as an Maximum Residue Limit (MRL) under the *Pest Control Products Act* for the purposes of adulteration provision of the *Food and Drugs Act*. Health Canada specifies science-based MRLs to ensure the food Canadians eat is safe.

The dietary risks from food and drinking water are expected to be negligible given the low toxicity, the lack of quantifiable residues from the supplemental residue information, and the likelihood (most likely negligible) that exposure of individuals to Problad Plus with lupine and/or other legume (for example, peanut) sensitivities will result in an allergic reaction. Consequently, the specification of an MRL under the *Pest Control Products Act* is not being recommended.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

For chemicals that are submitted under DIR2012-01 Guidelines for the Registration of Non-Conventional Pest Control Products, the data requirements follow a tiered approach. If information in Tier I demonstrates that the technical grade active ingredient is of low acute toxicity to the non-target organisms potentially exposed to the proposed products, Tier II information, which includes detailed information on the fate of the chemical, is not routinely required, as was in the case of Problad Technical Fungicide However, a ready biodegradability study was submitted. Although the ready biodegradability studies are normally not assessed by the EAD because the conditions of the study are not necessarily applicable to environmental conditions (sewage sludge inoculum is used instead of natural soil and/or water), this study was reviewed to qualitatively assess the potential persistence of Problad Technical Fungicide.

The ready biodegradability of Problad Technical Fungicide was assessed in mineral test medium which was inoculated with micro-organisms from a municipal wastewater for 28d in a closed bottle in the dark at 19.0 – 22.0°C. Problad Plus was applied at the rate of 2 mg a.i./L. The experiment was conducted in accordance with the OECD Guideline 301D, and in compliance with the OECD GLP standards. The test system consisted of glass bottles closed with ground in stoppers, filled with aerated and inoculated test medium. Measurements of O_2 consumption were done with an Oximeter and a calibrated electrode.

The percent biodegradation for Problad Plus was 65.9% in 4 days, 81.4% in 14 days and, 91.7% in 28 days. Therefore, Problad Plus is considered to be readily biodegradable.

4.2 Environmental Risk Characterization

The studies submitted did not show any adverse effects to the non-target organisms tested (beneficial arthropods, honeybees, earthworms). Waiver requests were submitted in lieu of studies on the acute toxicity to birds on the basis that sweet lupine (*Lupinus albus doce*) seeds have been widely used for feed for livestock (both mamalian and avian) with no reported adverse effects. Although no plant toxicity studies were submitted, Problad Plus was applied to a wide variety of plants (to determine efficacy of Problad Plus) with no ill effect to the plants.

Although toxicity data (studies or endpoints) to aquatic organisms were not available to the PMRA, the United States Environmental Protection Agency has assessed acute toxicity studies conducted with aquatic organisms (vertebrates and invertebrates) and considers Problad Plus to be non-toxic to aquatic organisms. As such, the weight of evidence suggests that Problad Plus is not likely to cause adverse effects to non-target aquatic organisms in the environment

Based on the low toxicity of BLAD in submitted laboratory studies, being a naturally occurring product, its history as a feed item (sweet lupines), and its rapid biodegradability, it can be concluded that Problad TGAI is not likely to cause adverse effects to non-target organisms in the environment.

5.0 Value

5.1 Acceptable Claims and Effectiveness Against Pests

5.1.1 Grape

Bunch rot: Trial results indicate that Problad Plus reduces bunch rot (*Botrytis cinerea*) incidence and severity under low to moderate disease pressure; the results were statistically comparable to the commercial standards included in the trials. Since there is a very low tolerance of bunch rot on fruit in production of either wine or table grapes, reduction of the incidence of bunch rot ensures a higher marketable yield. The value information was sufficient to support the claim of control of botrytis bunch rot.

Powdery mildew: On leaves, variability in the level of efficacy against powdery mildew was observed at all tested rates of Problad Plus. Efficacy could be quite low once disease pressures increased, especially when compared to the performance of the commercial standards. On fruit, similar effects were observed. Treatment with commercial standards resulted in significantly lower disease on fruit under higher disease pressure. Severe foliar infection can significantly reduce sugar accumulation in the fruit during veraison and also reduce vine vigour. Powdery mildew can stop grape growth and reduce fruit set if fruit infection occurs early in fruit development. Based on the performance of Problad Plus and the commercial standards in the trials, the claim of suppression of powdery mildew on grapes was supported.

5.1.2 Strawberry

Grey mould: Problad Plus significantly reduced the incidence of grey mould on strawberries at a level comparable to the commercial standards. Higher rates were more efficacious under moderate to high disease pressures. Trial reports suggest that the low rate of Problad Plus has poor residual control and is more appropriate for low disease pressure. Application on a 7-day interval is also recommended for higher disease pressure. Grey mould infection affects the economic value of strawberry crops both at harvest and in storage. The value information was sufficient to support the claim of control of grey mould.

Powdery mildew: Problad Plus significantly reduced the incidence and severity of powdery mildew on strawberries under low to moderate disease pressure. The commercial standards provided significantly higher control of both incidence and severity. Variability in the level of efficacy suggests suppression of powdery mildew. Infected flowers lead to poor pollination and poor fruit set. Infections on green fruit can stop ripening, and infected ripe berries may have a different texture and a somewhat flat or bitter taste making the fruit unmarketable. Problad Plus would be most appropriate for use when disease pressure is low or in alternation with conventional fungicides. The value information was sufficient to support the claim of suppression of powdery mildew.

5.1.3 Tomato

Grey mould: Problad Plus controlled grey mould (*B. cinerea*) at the low rate when disease pressure was low. At mid and high rates, control of incidence and severity was observed with moderate disease pressure. Although the level of efficacy expressed was variable, the results were comparable to the commercial standard. There is concern over disease resistance in tomato production and a need for new biological controls, especially for organic production. Since control of *B. cinerea* was also observed on grape and strawberry, it can be concluded that the product will also control grey mould on tomato.

5.1.4 Stone Fruit / Almond

Blossom blight, brown rot: Problad Plus demonstrated partial suppression of blossom blight when disease pressure reached higher levels. It was noted that the level of control expressed by Problad Plus, although statistically comparable to the standards, ranged from partial suppression to suppression (average levels of control suggest partial suppression). The standards resulted in suppression to control of blossom blight (average control expressed was suppression). Grower expectations of control claims are higher than the level of efficacy resulting from Problad Plus treatment. The claim of suppression is appropriate for this claim. Reduction of inoculum at the blossom stage will reduce secondary infections of fruit. No direct effect on fruit infection was demonstrated so the claim was supported for blossom blight only.

5.1.5Ornamentals

Grey mould: Problad Plus reduced the incidence of the grey mould (*B. cinerea*) in trials on grape, strawberry and tomato. Assessments were made on fruit in these trials, but infection likely

occurred through blossoms. Due to the ability of *Botrytis cinerea* to affect multiple crops in the same manner, data generated on grape, strawberry and tomato were extrapolated to support the claim on ornamentals.

5.2 Consideration of Benefits

BLAD polypeptide is a non-conventional fungicide that can be integrated into spray programs for both conventional and non-conventional growers. Use as a rotational product with conventional fungicides and cultural methods may reduce reliance on chemical pesticide applications.

5.3 Economics

No market analysis was done for this submission.

5.4 Sustainability

5.4.1 Survey of Alternatives

A number of fungicides are registered on the labelled crops to control or suppress plant diseases supported for registration on the Problad Plus label. Refer to Appendix I, Table 3 for further information on alternative products.

5.4.2 Compatibility with Current Management Practices Including Integrated Pest Management

The new mode of action of BLAD polypeptide has value as a rotational fungicide in an integrated pest management program. The active ingredient originates from a plant protein, so the product is not expected to negatively affect the efficacy of other pesticides when used as a rotational or tank mix partner. Problad Plus can also be applied up until harvest to allow disease control after the use of conventional products is no longer permitted.

5.4.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

BLAD polypeptide has a unique mode of action and an unknown risk for resistance development. The target pathogens (grey mould, powdery mildew, blossom blight) have a high risk for developing resistance to conventional fungicides. To reduce the risk of resistance development to Problad Plus, the label indicates the maximum number of sequential and seasonal applications for each crop and recommends alternating applications with other effective fungicides with a different mode of action. Alternate products are available for all use claims, so Problad Plus can be integrated into a disease management program with other fungicides to delay the possible development of resistance to BLAD polypeptide and the alternative products.

5.4.4 Contribution to Risk Reduction and Sustainability

BLAD polypeptide is a naturally occurring seed storage protein from the lupine, which grows in meadows and pastures. This biofungicide will contribute to sustainable agriculture due to its innocuous nature and unique mode of action.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy: persistent (in air, soil, water and/or sediment), bioaccumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, Problad Technical Fungicide and the related end-use product, Problad Plus, were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1criteria. It has been determined that these substances do not meet TSMP Track-1 criteria because:

• Problad Technical Fungicide is a naturally occurring substance that has a non-toxic mode of action and is not expected to be persistent or bioaccumulative in the environment. For these reasons, Problad Technical Fungicide and the related end-use product Problad Plus are not expected to be TSMP Track-1 substances.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[6]. The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[8], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act*

---

5 DIR99-03, The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy

6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

7 NOI2005-01, List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.

8 DIR2006-02, Formulants Policy and Implementation Guidance Document.

(substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Problad Technical Fungicide and Problad Plus do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02[9].

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for BLAD polypeptide is adequate to define the majority of toxic effects that may result from exposure to BLAD polypeptide. The active ingredient, BLAD polypeptide, is of low acute toxicity by oral, dermal, and inhalation routes. There was evidence of mild irritation to the skin and eyes of rabbits after acute dosing. BLAD polypeptide is not a dermal sensitizer. Waivers were granted for short-term toxicity, prenatal developmental toxicity, and genotoxicity on the basis of minimal exposure to individuals coming in contact with BLAD polypeptide. Bioinformatics, susceptibility to protease digestion, and serology study results demonstrate that individuals sensitive to allergens found in lupine and/or other legumes are unlikely to have an allergic response if exposed to Problad Plus. In addition, the proteins in lupine seed that are responsible for allergic reactions in sensitive individuals must not be present in Problad Technical Fungicide or Problad Plus.

Loaders, mixers, applicators, and workers are not expected to be exposed to levels of BLAD polypeptide that will result in an unacceptable risk due to exposure when Problad Plus is used according to label directions.

Inadvertent bystander exposure during application of Problad Plus may be minimized when the end-use product is only applied when the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools, and recreational areas is minimal. Applicators should take into consideration wind speed, wind direction, temperature, application equipment, and sprayer settings.

The dietary risks from food and drinking water are expected to be negligible. Consequently, the specification of an MRL under the *Pest Control Products Act* is not being recommended.

7.2 Environmental Risk

Based on the low toxicity of BLAD in submitted laboratory studies, being a naturally occurring product, its history as a food and feed item (sweet lupines), and its rapid biodegradability , it can be concluded that Problad TGAI is not likely to cause adverse effects to non-target organisms in

[9] DIR2006-02, Formulants Policy and Implementation Guidance Document.

the environment with the supported uses. Therefore, the risk to non-target organisms in the environment is considered to be negligible when this product is used according to label instructions.

7.3 Value

The value information submitted to register Problad Plus was adequate to demonstrate the value of this product and support its use on the supported crops and diseases.

Grey mould, powdery mildew and blossom blight reduce the vigour of plants and can cause fruit rot in the field or in storage. The yield and quality of stone fruits, almonds, grapes, strawberries and tomatoes may be significantly reduced as a result of infection. Problad Plus offers growers a non-conventional option for rotation with currently registered products as part of a disease management program. The short pre-harvest interval allows flexibility in the scheduling of this fungicide spray. Use of this product potentially reduces the number of applications of conventional fungicides and contributes to resistance management and sustainability.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Problad Technical Fungicide and Problad Plus, containing the technical grade active ingredient BLAD polypeptide, to be used against powdery mildew and grey mould of on grape, strawberry, tomato, stone fruit, almond and ornamental plants.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

♀	female
♂	male
ADI	acceptable daily intake
a.i.	active ingredient
ALS	acetolactate synthase
ARfD	acute reference dose
atm	atmosphere
β	Beta
BLAD	banda de *Lupinus albus* doce
bw	body weight
°C	degree Celsius
CAS	Chemical Abstracts Service
cm	centimetres
d	day
DF	dry flowable
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{75}	dissipation time 75% (the dose required to observe a 75% decline in concentration)
EASI	Eurofins Agroscience Services, Inc.
ELISA	enzyme-linked immunosorbent assay
EC_{10}	effective concentration on 10% of the population
EC_{25}	effective concentration on 25% of the population
EP	end-use product
ER_{25}	effective rate for 25% of the population
g	gram
g/mL	gram per millilitre
GLP	good laboratory practice
ha	hectare(s)
HDT	highest dose tested
Hg	mercury
HPLC	high performance liquid chromatography
hr	hour
hrs	hours
IUPAC	International Union of Pure and Applied Chemistry
kDa	kiloDalton
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
kg	kilogram
km	kilometre
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre
L/ha	liter per hectare
LC_{50}	lethal concentration 50%

LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOEC	low observed effect concentration
LOD	level of detection
LOQ	level of quantification
1/n	exponent for the Freundlich isotherm
LR_{50}	lethal rate 50%
MAS	maximum average score
MOE	margin of exposure
mg	milligram
MIS	maximum irritation score
mL	millilitre
MRL	maximum residue limit
MS	mass spectrometry
MW	molecular weight
N/A	not applicable
Nm	nanometre
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOER	no observed effect rate
N/R	not required
NZW	New Zealand white
O_2	oxygen
OC	organic carbon content
OD	optical density
OECD	Organisation for Economic Co-operation and Development
OM	organic matter content
PBI	plantback interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
RSD	relative standard deviation
SC	soluble concentrate
$t_{1/2}$	half-life
T3	tri-iodothyronine
T4	thyroxine
TGAI	technical grade active ingredient
TSMP	Toxic Substances Management Policy
TRR	total radioactive residue
UAN	urea ammonium nitrate
UF	uncertainty factor
µg	micrograms
UV	ultraviolet
v/v	volume per volume dilution
w/w	weight per weight dilution

Appendix I Tables and Figures

Table 1 Toxicity Profile of Problad Plus Containing BLAD Polypeptide
(Effects are known or assumed to occur in both sexes unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Sprague-Dawley rats (♀) PMRA #2280361	LD_{50} > 5000 mg/kg bw Low toxicity
Acute dermal toxicity Sprague-Dawley rats PMRA #2280362	LD_{50} > 2000 mg/kg bw Low toxicity
Acute inhalation toxicity (nose-only) Sprague-Dawley rats PMRA #2280363	LC_{50} > 5.34 mg/L Low toxicity
Dermal irritation NZW rabbits (♂) PMRA #2280365	MAS = 0.2/8 (24, 48, & 72 hrs), MIS = 2.3/8 (1 hr) At 1 hour, well-defined erythema and very slight edema was observed. Skin was normal at 48 hours. Mildly irritating
Eye irritation NZW rabbits (♀) PMRA #2280364	MAS = 7.9/110 (24, 48, & 72 hrs), MIS = 23.3/110 (1 hr) At 1 hour, marked conjunctival redness and discharge, as well as corneal opacity was observed. Eyes were normal at 72 hours. Mildly irritating
Dermal sensitization (Beuhler test) Hartley albino guinea pigs PMRA #2280366	Not a dermal sensitizer
Allergenicity and Potential Cross-Reactivity PMRA # 2280370, 2280371, 2280374, 2280375	The scientific literature provided claims that this product will not elicit hypersensitivity effects in the general population.

Study Type/Animal/PMRA #	Study Results
Serology Study PMRA # 2425204, 2425205, 2442107 to 2442131	Immunoblot assay did not produce any positive results (0/30) for Problad Plus in individuals who were sensitive to lupine and/or other legumes.
Short-term Oral Toxicity PMRA # 2280367	An unsolicited waiver request for Problad Plus was submitted and found to be acceptable on the basis of minimal exposure if the label directions and precautions are followed, as well as the fact that polypeptides are generally hydrolyzed and absorbed as amino acids on ingestion.
Short-term Dermal Toxicity PMRA # 2280368	An unsolicited waiver request for Problad Plus was submitted and found to be acceptable on the basis of minimal exposure if the label directions and precautions are followed.
Short-term Inhalation Toxicity PMRA # 2280369	An unsolicited waiver request for Problad Plus was submitted and found to be acceptable on the basis of minimal exposure if the label directions and precautions are followed.

Table 2 Toxicity Profile of Problad Technical Fungicide
(Effects are known or assumed to occur in both sexes unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity PMRA #2280361	The acute oral toxicity study submitted for the end-use product, Problad Plus, used BLAD polypeptide at the same concentration as proposed for Problad Technical Fungicide (20% a.i.). As such, the request to bridge the acute oral toxicity data from the end-use product to the technical grade active ingredient was considered acceptable. Low acute toxicity
Acute dermal toxicity PMRA #2280362	The acute dermal toxicity study submitted for the end-use product, Problad Plus, used BLAD polypeptide at the same concentration as proposed for Problad Technical Fungicide (20% a.i.). As such, the request to bridge the acute dermal toxicity data from the end-use product to the technical grade active ingredient was considered acceptable. Low acute toxicity
Acute inhalation toxicity PMRA #2280363	The acute inhalation toxicity study submitted for the end-use product, Problad Plus, used BLAD polypeptide at the same concentration as proposed for Problad Technical Fungicide (20% a.i.). As such, the request to bridge the acute inhalation toxicity data from the end-use product to the technical grade active ingredient was considered acceptable. Low acute toxicity

Study Type/Animal/PMRA #	Study Results
Eye irritation PMRA #2280364	The primary eye irritation study submitted for the end-use product, Problad Plus, used BLAD polypeptide at the same concentration as proposed for Problad Technical Fungicide (20% a.i.). As such, the request to bridge the primary eye irritation data from the end-use product to the technical grade active ingredient was considered acceptable. Mildly irritating
Dermal irritation PMRA #2280365	The primary skin irritation study submitted for the end-use product, Problad Plus, used BLAD polypeptide at the same concentration as proposed for Problad Technical Fungicide (20% a.i.). As such, the request to bridge the primary skin irritation data from the end-use product to the technical grade active ingredient was considered acceptable. Mildly irritating
Dermal sensitization PMRA #2280366	The dermal sensitization study submitted for the end-use product, Problad Plus, used BLAD polypeptide at the same concentration as proposed for Problad Technical Fungicide (20% a.i.). As such, the request to bridge the dermal sensitization data from the end-use product to the technical grade active ingredient was considered acceptable. Not a dermal sensitizer
Short-term Oral Toxicity PMRA # 2281869	The data requirement for short-term oral toxicity was waived on the basis that minimal exposure is expected if the label directions and precautions are followed, as well as the fact that polypeptides are generally hydrolyzed and absorbed as amino acids on ingestion.
Short-term Dermal Toxicity PMRA # 2281871	Although data were required for only one short-term toxicity study, the information submitted for the dermal route of exposure was assessed. The data requirement for short-term dermal toxicity study was waived on the basis that minimal exposure is expected if the label directions and precautions are observed.
Short-term Inhalation Toxicity PMRA # 2281872	Although data were required for only one short-term toxicity study, the information submitted for the inhalation route of exposure was assessed. The data requirement for short-term inhalation toxicity study was waived on the basis that minimal exposure is expected if the label directions and precautions are observed.
Prenatal Developmental Toxicity PMRA # 2281873	The prenatal developmental toxicity data requirement was waived on the basis that minimal exposure is expected if the label directions and precautions are followed, as well as the fact that polypeptides are generally hydrolyzed and absorbed as amino acids on ingestion.

Study Type/Animal/PMRA #	Study Results
Genotoxicity: bacterial reverse mutation assay PMRA # 2281874	The bacterial reverse mutation assay data requirement was waived on the basis that minimal exposure is expected if the label directions and precautions are followed, as well as the fact that polypeptides are generally hydrolyzed and absorbed as amino acids on ingestion.
Genotoxicity: *in vitro* mammalian cell assay PMRA # 2281875	The *in vitro* mammalian cell assay data requirement was waived on the basis that minimal exposure is expected if the label directions and precautions are followed, as well as the fact that polypeptides are generally hydrolyzed and absorbed as amino acids on ingestion.

Table 3 Registered Alternative Products for the Crops and Pests to be Registered on the Problad Plus Label

(Please Note that Some Active Ingredients May Not Be Registered on the Entire Crop Group [as of November 2013])

Crop	Disease	Active Ingredient (Mode of Action Group)
Grape	Powdery mildew (*Erysiphe necator* syn. *Uncinula necator*)	myclobutanil (3) tetraconazole (3) difenoconazole (3) boscalid (7) fluopyram + pyrimethanil (7+9) boscalid + pyraclostrobin (7+11) kresoxim-methyl (11) trifloxystrobin (11) quinoxyfen (13) *Bacillus subtilis* (44) metrafenone (U8) sulphur (M) copper (M) folpet (M) mineral oil (NC) potassium bicarbonate (NC) *Streptomyces lydicus* (NC) extract of *Reynoutria sachalinensis* (NC) garlic powder (NC) tea tree oil (NC)
	Botrytis bunch rot (*Botrytis cinerea*)	iprodione (2) fluopyram (7) fluopyram + pyrimethanil (7+9) boscalid + pyraclostrobin

Crop	Disease	Active Ingredient (Mode of Action Group)
		(7+11) cyprodinil (9) pyrimethanil (9) cyprodinil + fludioxonil (9+12) fenhexamid (17) extract of *Reynoutria sachalinensis* (NC)
Strawberry	Grey mould (*Botrytis cinerea*)	thiophanate-methyl (1) iprodione (2) penthiopyrad (7) boscalid + pyraclostrobin (7+11) pyrimethanil (9) cyprodinil + fludioxonil (9+12) fenhexamid (17) *Bacillus subtilis* (44) folpet (M) chlorothalonil (M) captan (M) thiram (M) *Trichoderma harzianum* (NC) *Streptomyces lydicus* (NC)
	Powdery mildew (*Podosphaera aphanis* syn. *Sphaerotheca macularis*)	myclobutanil (3) tetraconazole (3) fluopyram (7) boscalid + pyraclostrobin (7+11) trifloxystrobin (11) quinoxyfen (13) sulphur (M) *Streptomyces lydicus* (NC) extract of *Reynoutria sachalinensis* (NC) tea tree oil (NC) citric acid, lactic acid (NC)
Tomato	Grey mould (*Botrytis cinerea*)	iprodione (2) penthiopyrad (7) boscalid (7) boscalid + pyraclostrobin (7+11) pyrimethanil (9) cyprodinil + fludioxonil (9+12)

Crop	Disease	Active Ingredient (Mode of Action Group)
		fenhexamid (17) *Bacillus subtilis* (44) ferbam (M) chlorothalonil (M) *Trichoderma harzianum* (NC) *Gliocladium catenulatum* (NC) extract of *Reynoutria sachalinensis* (NC) hydrogen peroxide (NC)
Stone Fruit	Blossom blight (*Monilinia fructigena, M. laxa*)	iprodione (2) triforine (3) fenbuconazole (3) propiconazole (3) penthiopyrad (7) fluopyram (7) fluopyram (7) boscalid (7) boscalid + pyraclostrobin (7+11) cyprodinil (9) fenhexamid (17) sulphur (M) chlorothalonil (M) ferbam (M) thiram (M)
Almond	Blossom blight (*Monilinia fructigena, M. laxa*)	propiconazole (3)* penthiopyrad (7) fluopyram (7)
Ornamentals	Grey mould (*Botrytis cinerea*)	thiophanate-methyl (1) iprodione (2) trifloxystrobin (11) fenhexamid (17) *Bacillus subtilis* (44) chlorothalonil (M) captan (M) *Trichoderma harzianum* (NC)

Table 4 Use (Label) Claims Proposed by Applicant and Whether Acceptable or Unsupported

Use claim	Supported / Not Supported
Control of botrytis bunch rot (*Botrytis cinerea*) on grape at 1.5 – 3.3 L/ha (309 – 680 g a.i./ha) applied at early bloom, bunch pre-closure, veraison and ripening.	Supported as proposed.
Control of powdery mildew (*Erysiphe necator*) on grapes at rates of 1.5 – 3.3 L/ha (309 – 680 g a.i./ha) applied on a 7 – 10 day interval.	Supported as suppression at proposed rates and timings.
Control of grey mould (*Botrytis cinerea*) on strawberries at rates of 1.5 – 3.3 L/ha (309 – 680 g a.i./ha) applied on a 7 – 10 day interval.	Supported as proposed.
Control of powdery mildew (*Sphaerotheca macularis*) on strawberries at rates of 1.5 – 3.3 L/ha (309 – 680 g a.i./ha) applied on a 7 – 10 day interval.	Supported as suppression of powdery mildew (*Podosphaera aphanis* syn. *Sphaerotheca macularis*) at proposed rates and timings.
Control of grey mould (*Botrytis cinerea*) on tomato at rates of 1.5 – 3.3 L/ha (309 – 680 g a.i./ha) applied on a 7 – 10 day interval.	Supported as proposed.
Control of blossom blight, brown rot (*Monilinia* spp.) on stone fruit and almond at rates of 1.5 – 3.3 L/ha (309 – 680 g a.i./ha) applied at pink (white, red) bud, full bloom and petal fall.	Supported as suppression of blossom blight (*Monilinia fructigena, M. laxa*) at proposed rates and timings.
Control of grey mould (*Botrytis cinerea*) on ornamentals at rates of 1.5 – 3.3 L/ha (309 – 680 g a.i./ha) applied on a 7 – 10 day interval.	Supported as proposed.

References

A. List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
1.0 Chemistry	
2280356	2011, PROBLAD PLUS Product Identity and Composition, DACO: 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.5.12, 3.5.13, 3.5.15 CBI
2280357	2011, Problad Preliminary Analysis, DACO: 3.4.1 CBI
2280358	2011, Problad Physical and Chemical Characteristics: Color, Physical State, Odor, Oxidation/Reduction, Flammability, pH, Viscosity, and Density/Relative Density, DACO: 3.5.1, 3.5.11, 3.5.2, 3.5.3, 3.5.6, 3.5.7, 3.5.8, 3.5.9
2281860	2011, Problad TGAI Preliminary Analysis, DACO: 2.13.1, 2.13.2, 2.13.3 CBI
2281861	2011, Problad TGAI Physical and Chemical Characteristics, Color, Physical State, Odor, Density, DACO: 2.14.1, 2.14.2, 2.14.3, 2.14.6
2281862	2011, Problad TGAI Product Identity and Composition, Summary of Physical and Chemical Properties, DACO: 2.11.1, 2.11.2, 2.11.3, 2.11.4, 2.14.1, 2.14.2, 2.14.3, 2.4, 2.5, 2.6, 2.7, 2.9 CBI
2459908	2014, Storage Stability of Problab Plus Biochemical Fungicide, DACO: 3.5.10.
2.0 Human and Animal Health	
2280359	2011, Waiver Request from the Biochemical Registration Requirements For a Prenatal Developmental Toxicity Study in Rats, DACO: 4.5.3
2280360	2011, Waiver Request from the Biochemical Registration Requirements for Mutagenicity Testing (Bacterial Reverse Mutation, In vitro mammalian call assay), DACO: 4.5.4
2280361	2011, Problad Acute Oral Toxicity - Up and Down Procedures in Rats, DACO: 4.6.1
2280362	2011, Problad Acute Dermal Toxicity Study in Rats- Limit Test, DACO: 4.6.2
2280363	2011, Problad Acute Inhalation Toxicity Study in Rats- Limit Test, DACO: 4.6.3
2280364	2011, Problad Primary Eye Irritation Study in Rabbits, DACO: 4.6.4
2280365	2011, Problad Primary Skin Irritation Study in Rabbits, DACO: 4.6.5
2280366	2011, Problad Dermal Sensitization Study in Guinea Pigs (Buehler Method), DACO: 4.6.6
2280367	2011, Waiver Request from the Biochemical Registration Requirements for a 90-day Oral Feeding Study in Rats, DACO: 4.7.1

2280368 2011, Waiver Request from the Biochemical Registration Requirements for a 90-day Dermal Study in Rats, DACO: 4.7.3

2280369 2011, Waiver Request from the Biochemical Registration Requirements for a 90-day Inhalation Study in Rats, DACO: 4.7.6

2280370 2011, Potential Allergenicity of Lupine Seeds (*Lupinus* sp.) with Special Emphasis on BLAD, an Intermediate in the Breakdown Process of the Major Storage Protein during Germination of Lupine Seeds, DACO: 4.7.7

2280371 2011, Potential Allergenicity of Lupine Seeds (*Lupinus* sp.) with Special Emphasis on BLAD, an Intermediate in the Breakdown Process of the Major Storage Protein during Germination of Lupine Seeds, DACO: 4.7.7

2280374 2011, Potential Allergenicity of Lupine Seeds (*Lupinus* sp.) with Special Emphasis on BLAD, an Intermediate in the Breakdown Process of the Major Storage Protein during Germination of Lupine Seeds, DACO: 4.7.7

2280375 2011, Potential Allergenicity of Lupine Seeds (*Lupinus* sp.) with Special Emphasis on BLAD, an Intermediate in the Breakdown Process of the Major Storage Protein during Germination of Lupine Seeds, DACO: 4.7.7

2281863 2011, PROBLAD TGAI Request to Bridge Acute Oral Toxicity Study Results in Rats, DACO: 4.2.1

2281864 2011, PROBLAD TGAI Request to Bridge Dermal Toxicity Study Results in Rats, DACO: 4.2.2

2281865 2011, PROBLAD TGAI Request to Bridge Acute Inhalation Toxicity Study Results in Rats, DACO: 4.2.3

2281866 2011, PROBLAD TGAI Request to Bridge Primary Eye Irritation Study Results in Rabbits, DACO: 4.2.4

2281867 2011, PROBLAD TGAI Request to Bridge Primary Skin Irritation Study Results in Rabbits, DACO: 4.2.5

2281868 2011, PROBLAD TGAI Request to Bridge Dermal Sensitization Study Results in Guinea Pigs, DACO: 4.2.6

2281869 2011, PROBLAD TGAI PROBLAD TGAI Request for a Waiver from the Biochemical Registration Requirements for a 90-day Dermal Study in Rats, DACO: 4.3.1

2281871 2011, PROBLAD TGAI Request for a Waiver from the Biochemical Registration Requirements for a 90-day Dermal Study in Rats, DACO: 4.3.4

2281872 2011, PROBLAD TGAI Request for a Waiver from the Biochemical Registration Requirements for a 90-day Inhalation Study in Rats, DACO: 4.3.6

2281873 2013, PROBLAD TGAI Request for a Waiver from the Biochemical Registration Requirements For a Prenatal Developmental Toxicity Study in Rats, DACO: 4.5.2

2281874 2011, PROBLAD TGAI Request for a Waiver from the Biochemical Registration Requirements for Mutagenicity Testing (Bacterial Reverse Mutation), DACO: 4.5.4

2281875 2011, PROBLAD TGAI Request for a Waiver from the Biochemical Registration Requirements for Mutagenicity Testing (*In vitro* mammalian call assay), DACO: 4.5.5

2293338 2013, EPA DER for ProBlad, DACO: 12.5.2,12.5.3,12.5.4,12.5.9

2425204 2013, Evaluation of the Allergenic and Cross Allergenic Potential of the BLAD Polypeptide, DACO: 4.8

2425205 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide, DACO: 4.8

2425213 2014, Residue-Waiver for residue studies-7.4.1,2,4-Problad Plus, DACO: 7.4.1, 7.4.2, 7.4.5

2425214 2014, Magnitude and Decline of BLAD Residues Following Application of ProBLAD Plus to Grapes, Strawberries, and Tomatoes, DACO: 7.2.1, 7.4.1, 7.4.2, 7.4.5

2425215 2014, EASI Grape Trial S13-04129-01 (Environmental Data), DACO: 7.2.1, 7.4.1, 7.4.2, 7.4.5

2425216 2014, EASI Grape Trial S13-04129-02 (Environmental Data), DACO: 7.2.1, 7.4.1, 7.4.2, 7.4.5

2425218 2014, EASI Strawberry Trial S13-04129-04 (Environmental Data), DACO: 7.2.1, 7.4.1, 7.4.2, 7.4.5

2425219 2014, EASI TomatoTrial S13-04129-05 (Environmental Data), DACO: 7.2.1, 7.4.1, 7.4.2, 7.4.5

2425220 2014, EASI TomatoTrial S13-04129-06 (Environmental Data), DACO: 7.2.1, 7.4.1, 7.4.2, 7.4.5

2442108 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 2, DACO: 4.8

2442109 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 3, DACO: 4.8

2442110 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 16, DACO: 4.8

2442111 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 17, DACO: 4.8

2442112 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 23, DACO: 4.8

2442113 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 26, DACO: 4.8

2442114 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 27, DACO: 4.8

2442115 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 28, DACO: 4.8

2442116 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 29, DACO: 4.8

2442117 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 30, DACO: 4.8

2442118 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 30, DACO: 4.8

2442119 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 30, DACO: 4.8

2442120 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 30, DACO: 4.8

2442121 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 30, DACO: 4.8

2442122 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 30, DACO: 4.8

2442123 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 30, DACO: 4.8

2442124 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 30, DACO: 4.8

2442125 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 30, DACO: 4.8

2442126 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 30, DACO: 4.8

2442127 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 30

2442128 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 30, DACO: 4.8

2442129 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 30, DACO: 4.8

2442130 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 30, DACO: 4.8

2442131 2014, Evaluate the Allergenic and Cross-Allergenic Potential of the BLAD Polypeptide-Patient Serum 30, DACO: 4.8

3.0 Environment

2280378 2010, ProBladAssessment of the Ready Biodegradability With the Closed Bottle Test, DACO: 8.2.3.5.2

2280379 2010, ProBlad Assessment of the Side Effects on the Activity of the Soil Microflora, DACO: 8.5

2280380 2010, ProBlad Acute Toxicity to Earthworms Using and Artificial Soil Test, DACO: 9.2.3.1

2280381 2010, ProBlad Acute Oral and Contact Toxicity to Honeybees in the Laboratory, DACO: 9.2.4.1,9.2.4.2

2280382 2010, ProBlad Toxicity to the Aphid Parasitoid in the Laboratory-Rate Response Test, DACO: 9.2.6

2280383 2011, Waiver Request from the Biochemical Registration Requirements for Nontarget Insect Testing, DACO: 9.2.7

2280384 2011, Waiver Request from the Biochemical Registration Requirements for Acute Aquatic Organism Toxicity Testing, DACO: 9.3.2

2280385 2011, Waiver Request from the Biochemical Registration Requirements for Avian Acute Toxicity Testing (Acute Oral, Dietary), DACO: 9.6.2.1,9.6.2.4

2280386 2011, Waiver Request from the Biochemical Registration Requirements for Nontarget Plant Testing (Seedling Emergence, Vegetative Vigor), DACO: 9.8.2,9.8.4,9.8.5

2281876 2011, PROBLAD TGAI Request for a Waiver from the Biochemical Registration Requirements for Nontarget Insect Testing, DACO: 9.2

2281877 2011, PROBLAD TGAI Request for a Waiver from the Biochemical Registration Requirements for Acute Aquatic Organism Toxicity Testing (invertebrate, freshwater), DACO: 9.3.2

2281878 2011, PROBLAD TGAI Request for a Waiver from the Biochemical Registration Requirements for Acute Aquatic Organism Toxicity Testing (fish, freshwater), DACO: 9.5.2.1

2281879 2011, PROBLAD TGAI Request for a Waiver from the Biochemical Registration Requirements for Avian Acute Toxicity Testing (Acute Oral), DACO: 9.6.2.1

2281880 2011, PROBLAD TGAI Request for a Waiver from the Biochemical Registration Requirements for Avian Acute Toxicity Testing (Dietary), DACO: 9.6.2.4

2281881 2011, Request for a Waiver from the Biochemical Registration Requirements for Nontarget Plant Testing (Seedling Emergence), DACO: 9.8.4

2281883 2011, PROBLAD TGAI Request for a Waiver from the Biochemical Registration Requirements for Nontarget Plant Testing (Vegetative Vigor), DACO: 9.8.4

4.0 Value

2280348 2011, Efficacy and Phytotoxicity Data to Support Registration of ProBlad Plus in California, DACO: 10.1, 10.2.1, 10.2.3.1, 10.2.3.3(D), 10.3.1, 10.3.2(B)

2280353 2011, Supplemental Efficacy and Phytotoxicity Data to Support Registration of ProBlad Plus in California, DACO: 10.1, 10.2.1, 10.2.3.1, 10.2.3.3(D), 10.3.1, 10.3.2(B)

2280354 2013, Value-Summary-Ornamentals-10.1, 10.2.3.4, 10.3.1-Problad, DACO: 10.1, 10.2.3.2(D), 10.3.1

2280355 2013, ProBlad Plus Description of the Pest Problem, DACO: 10.2.2

2296396 2013, Value-10-Comparison of formulas-10april2013, DACO: 10.2.3.1, 10.3.1 CBI

2296397 2013, ProBlad Plus Formula comparison, DACO: 10.2.3.1,10.3.1 CBI

B. Additional Information Considered

Published Information

1.0 Chemistry

PMRA Document Number	Reference
2395333	Monteiro, S., Freitas, R., Rajasekhar, B. T., Teixeira, A. R., Ferreira, R. B. 2010. The unique biosynthetic route from Lupinus β-conglutin gene to Blad. PLoS ONE 5(1): e8542, doi:10.1371/journal.pone.0008542., DACO: 2.6